23 May 2025
EMA/CVMP/99773/2023
Committee for Veterinary Medicinal Products (CVMP)

Overview of comments received on 'Reflection paper on the application of Article 40(5) of Regulation (EU) 2019/6 for certain categories of variations' (EMA/CVMP/55240/2025)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	Access VetMed
2	AnimalhealthEurope

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	Access VetMed welcomes the CVMP reflections in this paper. Its intentions to elaborate more detailed scientific criteria to ensure a clear and consistent interpretation to the conditions set up in Art 40(5) of Regulation 2019/6, and so to improve predictability both for regulators and applicants, are very laudable and appreciated. Overall, we cannot report major issues we do not agree with, as the principles and ideas presented in the text are consensual. When considering its practical application, we find that the details and visibility of what should be done to obtain a claim are limited. The reflection paper provides several examples, which is helpful and appreciated, but does not recognise the merits on how product developments will be evaluated. It is understood that assessments will apply on a case-by-case basis; clear rules or recommendations on what should be included in the supportive dossier are not provided. As such, the basis on which decisions will be taken by regulators is ambiguous and does not give guarantees about equality for all potential applicants. In the end, we fear that implementation of Art 40(5) of Regulation 2019/6 may bring confusedness in the competitive market and become a tool for gradually restricting competition on the VMP market. We would like to reiterate the industry need for a clear and consistent interpretation of legislative provisions across EU in order to ensure predictability, and to prevent an arbitrary implementation.	A reflection paper is a document developed to communicate the current status of discussions, but it does not have the purpose to provide detailed guidance on regulatory, procedural or scientific issues. Therefore, no detailed guidance is provided. The 'Guidance to Applicants' (GtA) provides some additional clarification (section 6.4.3).

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1	The reflection paper suggests that, overall, the risk assessment should be quantitative. We welcome the fact that criteria should be designated based on quantifiable parameters whenever possible, in particular regarding "reduction" or "improvement", in order to be sure that the changes are significant against the prior product profile. It is paramount that criteria and methods applied provide irrefutable evidence that the use of a certain veterinary medicine is substantially and measurably contributing to the two objectives marked in Article 40(5). However, we are concerned that quantification may not be feasible in many cases, due to a lack of data on the reference product (which - in most cases - may have been authorised for a long time). We wonder how this limitation might be handled by the CVMP during the assessment process and reflection from CVMP in this regard in the paper would be welcome.	Overall, the risk assessment will be qualitative. Only in certain areas (e.g. user safety, environmental risk) quantitative elements will be taken into account. The RP has been reworded to make this clearer. The 'current guidance' documents referenced in the RP in relation to the AMR risk assessment for public and target animal health and for the environment do not require a quantitative approach to the overall risk assessment and it is agreed that this is unlikely to be available for the reference product. However, there is the possibility to provide relevant quantitative studies to support individual elements of the overall risk estimation.
2	AnimalhealthEurope is grateful for the opportunity to comment on this reflection paper and appreciates the CVMP's efforts to bring clarity to the interpretation of article 40(5). The reflection paper provides this on a number of important points, where the CVMP interpretation is supported by AnimalhealthEurope. Never-the-less, as a general overview, AnimalhealthEurope considers CVMP's interpretation of article 40(5) to be overly restrictive, especially in the context of recitals 33 and 36. However, we appreciate that product developments involving a change to the pharmaceutical form, administration route or dosage that also include associated changes, e.g. target species, are not	To be considered under Art 40(5), a variation must include a change of the dosage, pharmaceutical form or route of administration of the already authorised product, which might be associated with another change, e.g. addition of a target species. If only a new target species is introduced, without any of these changes, this would not qualify for such a variation. The same dose (or any dose) used in a new target species cannot be considered a new dosage itself.

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	excluded from the application of article 40(5), provided that the conditions are met. In this respect we request confirmation that in the case of addition of target species, the posology for the new target species itself can be considered as a change to the dosage (even if it is the same or falls within the range of the posology for the target species already included in the marketing authorisation). **Justification**: Pre- clinical studies and clinical trials have to be done in the additional target species, even if the final dosage is the same or falls within the range of the posology for a target species already included in the marketing authorisation.	
2	**Pre-submission meetings foreseen to discuss the potential eligibility of protection of technical documentation under article 40(5)** The Introduction (lines 47-48) states that regulatory considerations are not included in the reflection paper. However regulatory guidance is **very much needed**. Several questions need to be answered in the short term. Therefore we request whether pre-submission meetings are foreseen to discuss the potential eligibility of protection of technical documentation under article 40(5) for the concerned innovation? It would be very helpful if CVMP would foresee a mechanism to seek specific advice on whether a new study could be eligible for the 4-years protection.	A reflection paper is a document developed to communicate the current status of discussions, but it does not have the purpose to provide detailed guidance on regulatory, procedural or scientific issues. Therefore, no detailed guidance is provided. As for any variation application, applicants may request a pre-submission meeting prior to the submission of their variation (see link). It should be noted that the confirmation whether the conditions under Art. 40(5) are met for a particular application is dependent upon the assessment by CVMP/NCAs (please refer also to the GtA). Therefore, a pre-submission meeting is not considered suitable to advise on the potential outcome of such an assessment.

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	Request: Please clarify the opportunity for pre-submission meetings or other specific advice and who assesses whether the criteria of article 40(5) are met (in case of DCP: only RMS?)?	
2	The concept that a reduction of the *risk* relating to the development of resistance is sufficient to meet criterion (a) of Article 40(5) is fully supported; however, it should be possible to demonstrate a reduction in risk through written justification and reasoning. The need for quantitative data, allowing a comparison of the proposed changes with the already authorised product, seems very limiting.	Please note that in relation to a reduction in AMR, Section 4.1 states: ***In particular cases it may be possible to base the demonstration of reduction in antimicrobial resistance risk on established and well substantiated models or concepts, duly justified through scientific evidence.*** *However, following a comparative approach to demonstrate a reduction of the risk of development of resistance* ***should not preclude the applicant to provide additional quantitative data*** *supporting an absolute reduction in resistance (e.g. MIC studies, or novel approaches), as these can be part of the suite of studies that support the overall risk estimation.* Hence there is no proposal that provision of quantitative data is an absolute requirement. Likewise, for antiparasitic products, the provision of appropriate bibliographic data relevant to the specific case to substantiate a decrease in the risk of development of antiparasitic resistance is also possible. Such approach should be duly justified and supported by adequate scientific literature. Product-specific quantitative data are only required where this is not the case (Section 4.2).
2	With regard to criterion b) of Article 40(5), for "improvement of the risk-benefit ratio", its application seems to be strictly limited,	The description of 'additional benefit' is directly linked to the Benefit-Risk guideline (EMA/CVMP/248499/2007 -

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	excluding additional benefits that are not directly linked to the claim of the product (e.g. palatability or long-acting).	Rev.1) where it is explained that *Additional benefits* are positive effects that are **not** specifically captured by the indication of the product…. However, the reflection paper also states that "*For an improvement of the benefit-risk balance via an additional benefit to be sufficient in the context of Article 40(5) it should be* ***meaningful*** *and* ***not result in an undue increase in risk.***" without excluding any type of additional benefit.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
047-48	1	**Comment**: Many doubts and practical questions of regulatory nature have been posted, namely on the additional 4 years of protection are granted to an existing MA and impact on a competitive VMPs market, i.e. Which mechanisms will be adopted to disclose to the public the granted periods of exclusivity? What impact on equivalent or essentially similar VMPs (reference or generics, as applicable)? **Proposed change**: It is acknowledged that it is not the remittance of the CVMP to provide a solution to these questions, and that regulatory considerations are not in the scope of this reflection paper. We would then be supportive to regulatory instrument to provide the necessary clarity and information for parties interested in implementing Article 40(5).	Not accepted. A reflection paper is a document developed to communicate the current status of discussions, but it does not have the purpose to provide detailed guidance on regulatory, procedural or scientific issues. Therefore, no detailed guidance is provided. The 'Guidance to Applicants' (GtA) provides some additional clarification, alongside guidance from the CMDv or EMA.
082-93	1	**Comments**: Product developments (AMR reduction and risk-balance improvements) on generic hybrid applications enhance the number of upgraded products for veterinarians to work with. In such cases, variations also require studies that could comply with criteria in art 40(5) and such studies / data are also eligible for the purpose of applying Article 40(5).	Not accepted. The Regulation does not restrict the application of Art. 40(5) to MAs granted under certain legal bases. However, addressing this point is outside the scope of this reflection paper.

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		Access VetMed suggests adding a clear statement that protection for studies that support generic hybrid registrations (referring to an existing marketing authorisation) are also in the scope of this reflection paper. **Proposed change:** To include a reference in this paragraph that all types of marketing authorisations for existing products are eligible to implement the provisions in Article 40(5), independently of their route of registration: new MA (Art 8), generic (Art 18), hybrid (Art 19).	
220-253	1	**Comments**: The criterion reduction in the antiparasitic resistance seems rather vague and unexplored. Applicants currently do not always know how to characterize/evidence resistance depending on the parasite because it is more complex to identify than for antimicrobials. Consequently, it is much more difficult to prove a reduction in the risk of resistance. The example quoted in the section "Example of a potential approach" are also not comforting: expansive specific clinical studies seem to be required; besides cost considerations, the design of such studies or the option of alternative/innovative ways may finally lead to many uncertainties.	Not accepted. It is acknowledged that the characterisation of antiparasitic resistance bears more complexity than the one of antimicrobial resistance. The information included in the reflection paper is based on the current scientific knowledge; however, it is expected that the knowledge in this area will evolve. To take account of this aspect, a range of possibilities to demonstrate the reduction in the risk of development of antiparasitic resistance are listed in the reflection paper, so that the applicants could select the best option applicable to their specific situation. In this respect, the reflection paper does not indicate that specific clinical trials are mandatory; the reduction in the risk of development of resistance can be demonstrated by providing either meaningful scientific literature data relevant for the specific case, conducting clinical trials showing a decreased resistance, or performing different types of studies showing

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			an improved level of efficacy. Some changes have been implemented in the reflection paper in order to make these aspects clearer.
237	2	**Comment:** '*because of the lower and more variable bioavailability…*' While it is acknowledged that topical products might lead to more variable bioavailability compared to injectable (or oral) formulations in cattle, more caution should be taken to state 'lower', as the doses in topical products and injectable products are often different. We suggest it is not prudent to make this high-level comparison between different formulations and different doses. **Proposed change:** 'because of the ~~lower and~~ more variable bioavailability…'	Accepted. The text has been amended accordingly.
244	2	**Comment:** '*Long-acting formulations may be associated with an increased risk of resistance selection*.' This is a very general and high-level statement assuming that all long-acting formulations have a very long tail of decreasing exposure. Long-acting formulations able to provide a high level of exposure that is sufficient to have high efficacy and a short PK/exposure tail, should not be considered to be more associated with the development of resistance than a short acting product with a short PK/exposure tail.	Accepted. The respective sentence has been amended to take account of the aspect highlighted by the stakeholder.

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		Proposed change: Provide more information on which PK/exposure profiles provide a higher risk for the development of resistance.	
258-259	2	**Comment:** '*This should ideally be assessed in an appropriately designed field trial*.' It might be questioned if it is appropriate to develop/push resistance in the field in order to demonstrate the benefit of a new formulation, especially if resistance is not yet existing or widespread. **Proposed change:** 'This should ideally be assessed in an appropriately designed field trial, although the risk of introducing resistant strains should be considered.'	Partly accepted. The text has been amended to take account of the risk of resistance development following the use of the already authorised product in such a clinical trial.
260	2	**Comment:** '*since this is likely to require substantial investment'*. It will not only require substantial investment, but also time to achieve resistance in the field. **Proposed change:** since this is likely to require substantial time and investment'.	Accepted. The text has been amended accordingly.
292-294	2	**Comment:** '*However, this type of study is associated with several challenges, including the identification of the relevant parasite isolate(s) and how the level of efficacy measured for the product development should be interpreted*.'	Accepted. The sentence has been deleted.

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		It is unclear what exactly the challenge is that is put forward in this statement. It can be argued that a laboratory study in which the previous product has an efficacy (based on worm counts) below the defined efficacy threshold while the new product has an efficacy above the efficacy threshold could be readily interpreted. The same applies to the identification of resistant isolates. Several GI nematode strains that are resistant to specific compounds have been isolated from the field. **Proposed change:** remove the sentence between lines 292 and 294 or provide more details about what the challenges actually are.	
294-296	2	**Comment:** '*It could also be challenging to determine whether the product development is at risk of selecting for a higher level of resistance.*' This statement is not clear. **Proposed change:** please provide more detail about what the challenges actually are and please clarify the meaning of this statement.	Partly accepted. The sentence has been deleted to avoid unclarity.
333-341	1	**Comment**: It is understood that the addition of a new target species per se may also be considered as meeting the criteria, when conditions set up in the reflection paper are also met: 'for which there are currently no treatment options available for the disease, provided that the contribution of the change of pharmaceutical form, route of administration or	Not accepted. Addition of a new target species ***per se*** cannot be considered as an improvement of the benefit-risk balance according to Art. 40(5)(b). A change of pharmaceutical form, administration route or dosage may also be associated with another variation. In order to meet criterion (b) of Art. 40(5) it is always necessary to justify how the change to the

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		dosage towards fulfilling the unmet medical need is substantiated'. This has been subject of debate in the past, confirmation would be welcome.	pharmaceutical form, administration route or dosage contributes to the claimed improvement of the benefit-risk balance and/or the reduction of resistance.
345-355	1	**Comment**: Are some reductions in risk considered more important than others? For example, would a reduced risk in the environmental impact of a herd treatment be considered more important than a reduced risk in environmental impact of a spot-on treatment for a household pet, meaning that a small reduction in risk would be 'meaningful' for the former but not for the latter? **Proposed change:** Further guidance on what constitutes a meaningful reduction in risk would be beneficial.	Not accepted. The scope of the reflection paper is not to provide detailed guidance on assessment issues. The benefits and risk for each product will be assessed on an individual basis taking into consideration the specific situation in each case.
349-355	1	**Comment**: the reflection paper sets that *"For example, a change of pharmaceutical form leading to better treatment compliance through, for example, increased ease of administration, could be considered to improve the benefit-risk balance, if the issue of non-compliance was already reported as a known risk from use in the field prior to the new product development".* In other words, it is understood that the claim would not be accepted if MAHs do not find any literature reference, which is very restrictive (even impossible). IN most cases, MAHs are informed about possible compliance problems through practitioners/pharmacovigilance cases (eventually),	Accepted. Reference to other sources of information (e.g. pharmacovigilance) has been added.

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		but not by means of peer-reviewed papers published on the topic. Therefore, it does not seem to be realistic. Similarly, there should be a significant decrease of the exposure to a toxic ingredient to claim for a decreased risk to the user: while this is agreed, how to define a margin of significant/not significant decrease that will be accepted by authorities? **Proposal**: Further guidance and clarification on how to substantiate and quantify a decrease of risk based on data or published literature would be welcome. This would improve the predictability and transparency (level playing field) for the assessment for all potential applicants.	
370-374	1	**Comment**: The wording "generally" in this statement: 'change to the withdrawal period is generally not considered to be a risk that could be reduced', indicates that the possibility exists that a change to the withdrawal period could qualify. **Proposed change**: "a change to the withdrawal period is generally not considered to be a risk that could be reduced; **considerations will be taken on a case-by-case basis".**	Partly accepted. The word 'generally' has been deleted.